



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
NATIONAL CENTER FOR ENVIRONMENTAL ASSESSMENT  
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OFFICE OF  
RESEARCH AND DEVELOPMENT

**MEMORANDUM**

**SUBJECT:** Review of Interim Pathology Report in Mice from 90-day  
Immunotoxicity Studies

**FROM:** Annie M. Jarabek *[Signature]*  
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RTP (MD-52)

**TO:** EPA Perchlorate Health Assessment Team

I have reviewed the interim histopathology report received on January 13, 1999 for the mice from the immunotoxicity studies ongoing at the Medical Center of South Carolina (Warren, 1999). These are reported for two 90-day experiments ("A" and "D") and only for the control and high-dose groups. Thus, this analysis is preliminary and limited but nevertheless worthwhile to include at this time since it may add some perspective on interspecies sensitivity. The report is attached.

Three histologic sections (A,B,C) from different levels of the thyroid gland were prepared and submitted for potential histopathologic assessment. Initially, all sections were examined to select the best single section for detailed evaluation. For consistency in the selection of the region of thyroid gland for the detailed evaluation, only sections of the thyroid tissue that contained parathyroid gland were used, when possible. If parathyroid gland was not present, the specimen with the largest area of thyroid gland was used. The study pathologist did not read the slides blind, but rather as he notes in the E-mail attached to the report, read the control and high dose specimens to detect a putative morphologic alteration and to characterize the full range of the alterations. Although I understand these points, no mention of a second pathologist to provide QA (per typical NTP SOP) on the study was mentioned. I expect the issue that we have already raised regarding the lack of QA or blind assessment will be resolved in the disposition of the decision regarding a potential pathology working group (PWG) of all the thyroid histopathology, so that I will not belabor the point herein.

In both 90-day experiments ("A" and "D"), the incidence of lesions induced by treatment were 0 in the control and 100% in the 30 mg/kg-day group. Lesions consistent with our proposed mode-of-action were observed, including: colloid depletion, congestion, hypertrophy. Mean values for these lesions are given but the

severity range was not provided. The majority of follicles tended to be smaller (a few exceptions on the periphery) with less colloid. The nuclear to cytoplasmic ratio of the follicular cells was usually 1.5 to 2.0.

These lesions in mice are consistent with those seen in the other species tested and with the proposed mode-of-action for the assessment model. Quantitative interspecies comparison is precluded at this time due to the lack of completed histopathology at the other doses. The Caldwell et al. (1995) study in rats is the only one that tested as high as approximately 22 mg/kg-day, but the difference in severity ratings and lack of statistics for both reports prevents further analysis. In the rabbit developmental study, histopathology was observed at the 30 mg/kg-day dose and this was not the lowest observed effect level. The best data for comparison may be the pending histopathology in the adults of the 2-generation reproductive study in rats, since there was a 30 mg/kg-day testing dose.

In conclusion, this preliminary analysis suggests that the mode-of-action is similar in mice, rabbits and rats. Quantitative interspecies comparison awaits dose-response data in the mice (i.e., histopathology for the remaining dose groups) and possibly a systematic pathology working group (PWG) evaluation of all the histopathology data once they are available.

Attachment